Diuretics and electrolyte disturbances in 1000 consecutive geriatric admissions

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Summary

Old people are commonly receiving diuretics on admission to hospital. Diuretics are recognized as a risk factor for electrolyte disturbances; controversy exists about the relative risks of different combinations (in particular, co-amilozide [Moduretic]). We recorded the drug history and serum electrolytes in 1000 consecutive admissions to a geriatric hospital, and examined the relative prescribing rates of various diuretics in the community.

Full results were obtained in 929 patients. A history of diuretic prescription was present in 353 (38%) of the patients; the mean serum sodium in this group (95% CI 136.0-137.1 mmol/l) was lower than in the 586 not prescribed diuretics (137.1-137.9 mmol/l). The difference was small but statistically significant (95% CI difference=0.3-1.6 mmol/l; $P<0.01$).

Hyponatraemia (serum sodium <130 mmol/l) was not significantly commoner in the 41 patients prescribed co-amilozide than in patients prescribed other diuretics. In general patients prescribed potassium-retaining diuretics had a lower serum sodium than the others.

There was a significant positive correlation between the serum potassium and the log[serum urea] ($r=0.26$, $P<0.001$) and a weak negative correlation existed between sodium and potassium ($r=-0.14$; $P<0.001$). There was an association between the prescription of potassium-retaining diuretics and a higher serum potassium; also an association between the prescription of a loop or thiazide diuretic and a lower serum potassium. These interactions were shown by multiple regression analysis to be independent and additive.

Co-amilozide formed a significantly higher proportion of all diuretics prescribed in the community group than in the inpatient group (18% versus 12%; $P<0.05$).

Hyponatraemia was mild and mainly associated with potassium-retaining diuretics in our patients. Our study was unable to confirm or refute any specific dangers of co-amilozide compared with other potassium-retaining diuretic combinations.

Introduction

Diuretic therapy is commonly prescribed in elderly patients for a number of conditions ranging from postural ankle swelling to severe heart failure; most prescriptions are initiated by the general practitioner[1]. Diuretics are a recognized risk factor in the genesis of renal impairment and electrolyte disturbances especially in the elderly[2] and in one study diuretics were the commonest cause of adverse drug reactions in the elderly[3]. Morbidity and even mortality can result from inappropriate or over-aggressive treatment[4], but the true magnitude of all these risks is unknown. Co-amilozide (hydrochlorothiazide 50 mg and amiloride 5 mg [Moduretic]) is claimed to be more likely than other diuretic combinations to cause metabolic problems in general[5], and hyponatraemia in particular when prescribed to elderly patients. This claim was originally based on the report by Sunderam and Mankikar[6], but their study did not allow for the prevalence of usage of co-amilozide in the community, which could potentially bias the results; there is evidence that co-amilozide is one of the more commonly prescribed thiazide/potassium-retaining combination diuretics in the community[1].

Our study set out firstly to compare the association between types of diuretic and serum electrolyte disturbances in patients admitted to an acute geriatric hospital, and secondly to examine the prevalence of prescription of diuretics in the local community.

Methods

One thousand consecutive patients admitted to one geriatric hospital were included in the study. Admission criteria included being over 65 years old and living in the Borough of Wandsworth; the only exclusions being acute gastrointestinal haemorrhage or acute surgical problems. The drug history on admission, age, sex, eventual outcome (death, discharge or transfer) and serum concentrations of sodium, potassium and urea from a venous blood sample were recorded.

Statistics for the prescribing of diuretics in the community during one month of the study were obtained from the local Family Practitioner Committee. An estimate of relative prescribing rates for various diuretic preparations in the local community during that month was derived from this information.

The results were stored on a computer database (dBase III); statistical analysis was undertaken using a standard statistical package (SPSS/PC+). All sodium and potassium values are in mmol/l and expressed as 95% confidence interval for the mean. Unpaired *t*-tests were used to examine differences between means of normally-distributed continuous data. Urea results were log transformed to achieve normal distribution[7]. Chi-squared tests were used for comparisons between categorical data and multiple regression analysis was used to measure interrelationships between variables in the study sample. A two-tailed *P* value of less than 0.05 was regarded as significant.

Results

The serum sodium and potassium results together with a full drug history were available for 929 (93%)

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of the 1000 patients studied. The mean age in these 929 patients was 82.6 (SD 6.9) years, 68% were female, 38% had a positive history of diuretic therapy prescription prior to admission and 15% died during their admission. These characteristics were not statistically significantly different from the age (81.1±7.7 years), sex distribution (62% female), positive diuretic history (32%) or mortality (23%) of patients without biochemical data available.

Sodium

The mean serum sodium was lower in the 353 (35%) patients prescribed any diuretic (whether potassium-retaining or not: 95% CI 136.0-137.1 mmol/l) compared with the 586 patients not prescribed any diuretics (137.1-137.9 mmol/l; 95% CI difference 0.3-1.6; $P<0.01$). Table 1 shows the most frequently prescribed diuretics in the inpatient group. The mean serum sodium for patients receiving frusemide, cyclopenthiazide/potassium and co-amilozide was significantly lower than for the non-diuretic group. The mean serum sodium was significantly higher for bumetanide/potassium compared to the non-diuretic group. Hyponatraemia (serum sodium < 130 mmol/l as defined by Sunderam[6]) was present in 6.9% of all patients and 3.4% of all patients were hyponatraemic and receiving a diuretic. Although the incidence of hyponatraemia was higher in the 41 patients prescribed co-amilozide compared with the 312 patients on non-co-amilozide diuretics, this difference failed to reach statistical significance (15% versus 8%; $\chi^2=1.06$, d.f.=351, $P>0.05$). The mean serum sodium in patients prescribed any potassium-retaining diuretic (134.8-136.3 mmol/l; $n=171$) was significantly lower than in the group prescribed no potassium-sparing therapy (137.0-137.8 mmol/l; $n=608$, $P<0.01$) and also lower than in the group prescribed potassium supplementation (136.9-138.5 mmol/l; $n=154$, $P<0.01$); these differences were also apparent within each of the groups of patients prescribed no diuretics, loop diuretics and thiazide diuretics. Table 2 shows the proportions of degrees of hyponatraemia in each group. Three patients had a serum sodium concentration of less than 120 mmol/l; two were not prescribed diuretics, (each 116 mmol/l) and one was (117 mmol/l).

Potassium

There was no significant difference in mean serum potassium between patients prescribed any diuretics

Table 1. Analysis of diuretics prescribed to elderly patients admitted to hospital

			Serum sodium concentration	
Diuretic	*Number*	*Percentage*	*95% CI for mean (mmol/l)*	*t value*
Nil	586	—	137.1-137.9	
Frusemide	128	36	135.3-137.1**	2.67
Bumetanide/KCl	80	23	137.6-139.8*	2.17
Cyclopenthiazide/KCl	44	13	134.2-137.4*	2.21
Co-amilozide	41	12	133.6-136.4**	3.20
Co-amilofruse	22	6	133.3-138.1	
Bendrofluazide	17	5	135.1-139.4	
Hydrochlorothiazide/triamterene	7	2	137.6-140.4	
Others	14	4		
Total	353	100	136.0-137.0*	2.93

*$P<0.05$; **$P<0.01$, compared with no diuretic group (two-tailed)

Table 2. Frequency distribution of serum sodium after stratifying by diuretic class and potassium sparing therapy

			Serum sodium (mmol/l)			
Diuretic/potassium-sparing therapy		*Number*	*<120-129*	*130-134*	*135-145*	*>145*
Nil	+nil	579	33 (5.7%)	86 (15%)	443 (77%)	17 (2.9%)
	+KCl	7	—	—	7	
	+P-RD	8	2	4	2	—
Thiazide	+nil	16	1	4	11	—
	+KCl	97	5 (5%)	12 (12%)	73 (75%)	7 (7%)
	+P-RD	114	13 (11%)	22 (19%)	77 (68%)	2 (2%)
	+both	3	—	—	3	—
Loop	+nil	13	—	4	9	—
	+KCl	49	5 (10%)	13 (27%)	29 (59%)	2 (4%)
	+P-RD	47	6 (13%)	11 (23%)	30 (64%)	—
	+both	2	—	—	2	—
Both	+KCl	1	—	—	1	—
	+P-RD	2	—	1	1	—
	+both	1	—	—	1	—
Total		939	65 (6.9%)	157 (17%)	689 (73%)	28 (3%)

KCl=potassium supplementation; P-RD=potassium-retaining diuretic; Percentages in parentheses for groups with at least 40 cases

Table 3. Frequency distribution of serum potassium after stratifying by diuretic class and potassium sparing therapy

Diuretic/potassium-sparing therapy		Number	Serum potassium (mmol/l) <3.0	3.0-3.4	3.5-5.0	5.1-6.0	>6.0
Nil	+nil	575	20 (4%)	86 (15%)	449 (78%)	19 (3%)	1 (0.2%)
	+KCl	7	1	1	4	1	—
	+P-RD	8	1	1	5	1	—
Thiazide	+nil	16	4	5	7	—	—
	+KCl	95	1 (1%)	21 (22%)	69 (73%)	4 (4%)	—
	+P-RD	113	—	9 (8%)	88 (78%)	12 (11%)	4 (4%)
	+both	3	—	—	3	—	—
Loop	+nil	13	2	5	6	—	—
	+KCl	48	2 (4%)	12 (25%)	32 (67%)	1 (2%)	1 (2%)
	+P-RD	46	3	5	32	4	2
	+both	2	—	—	1	1	—
Both	+KCl	1	—	1	—	—	—
	+P-RD	2	—	—	2	—	—
	+both	1	1	—	—	—	—
Total		930	8 (1%)	43 (5%)	698 (75%)	146 (16%)	35 (4%)

KCl=potassium supplementation; P-RD=potassium-retaining diuretic; Percentages in parentheses for groups with at least 40 cases

Table 4. Mean serum potassium (expressed as 95% confidence interval) stratified by potassium sparing therapy and serum urea

Potassium-sparing therapy		Stratified by serum urea (mmol/l) <7.5	7.5-14.9	15.0-19.9	20.0-24.9	>25
+Nil	3.85-3.95 (607)	3.85-3.95 (332)	3.92-4.08 (226)	3.81-4.22 (226)	3.56-5.24 (8)	3.81-5.19 (14)
+KCl	3.69-3.91 (154)	3.56-4.04 (58)	3.69-3.91 (84)	2.25-5.75 (84)	3.09-5.31 (4)	2.37-6.83 (4)
+P-RD	4.18-4.42 (169)	3.86-4.14 (48)	4.06-4.34 (79)	4.19-5.01 (21)	3.59-5.81 (7)	4.43-5.57 (14)
+Both	3.46-5.34 (6)	—	3.16-5.64 (5)	—	—	4.5 (1)
Total	3.96-4.04 (936)	3.84-3.96 (438)	3.94-4.06 (394)	3.98-4.42 (52)	4.02-4.98 (19)	4.32-5.08 (33)

KCl=potassium supplementation; P-RD=potassium-retaining diuretic; The number in each group is given in parentheses

(3.9-4.1 mmol/l; $n=348$) and patients prescribed no diuretics (3.9-4.0 mmol/l; $n=582$). For analysis of serum potassium by diuretic class see Table 3. There was no significant difference in mean serum potassium between those patients not prescribed any potassium-sparing therapy (3.9-4.0 mmol/l; $n=604$) and those prescribed potassium supplementation (3.7-4.0 mmol/l; $n=151$). There was a highly significant difference ($P<0.001$) in mean serum potassium between these two groups and the group of patients prescribed potassium-retaining diuretics (4.1-4.4 mmol/l; $n=169$). There was a weak, but statistically significant, negative correlation between serum sodium and serum potassium ($r=-0.14$, $P<0.001$).

Urea

Patients with no significant renal failure (serum urea $\leqslant 15$ mmol/l) had a lower mean serum potassium concentration (3.9-4.0 mmol/l; $n=825$) than those with significant renal impairment (serum urea >15 mmol/l: 4.3-4.6 mmol/l; $n=102$; $t=7.56$, $P<0.001$). Patients in the latter group had statistically significantly higher mean serum potassium concentration whether on no potassium sparing therapy, potassium supplementation, or potassium-retaining diuretics. After stratifying patients by serum urea, there was no difference in the mean serum sodium but the mean serum potassium increased with the urea. Table 4 shows the relationship between mean serum potassium, potassium-sparing therapy and serum urea. The mean serum potassium increases across the rows and also down the columns, suggesting an additive effect. Multiple regression analysis using the normally distributed log[serum urea] confirmed this.

Survival

Contingency tables were drawn up comparing mortality with the presence of hyponatraemia, hypokalaemia (<3.0 mmol/l), uraemia (>14.9 mmol/l), whether or not prescribed diuretics, and whether or not prescribed potassium-retaining diuretics. Chi-square testing showed no association between mortality and any of the variables except urea, which showed a significant association ($\chi^2=14.9$; d.f.=1, $P<0.001$) increasing with greater degrees of uraemia.

The data about local community prescribing showed that 20 656 prescriptions for diuretics were written by general practitioners in May of the study year. Table 5 shows the frequency distribution. Co-amilozide represented a higher proportion of diuretics prescribed in the community group than in the inpatient group (18% versus 12%; $P<0.05$).

Discussion

Hyponatraemia is common in ill patients presenting to hospital[8]. There is evidence that the renal (both

Table 5. Frequency distribution of diuretics prescribed in the community during one month

Diuretic	*Number*	*Percentage*
Cyclopenthiazide/KCl	5251	25.4
Co-amilozide	3846	18.6
Frusemide	3071	14.9
Bumetanide/KCl	1824	8.8
Bendrofluazide	1597	7.7
Co-amilofruse	859	4.2
Hydrochlorothiazide/triamterene	360	1.7
Amiloride	42	0.2
Bendrofluazide/KCl	484	2.3
Indapamide	411	2.0
Frusemide/KCl	367	1.8
Others	2544	12.3
Total	20 656	100

glomerular and tubular) and neuro-endocrine changes which occur in normal aging, render the kidney less able to maintain homeostasis under a variety of insults, including diseases and drugs[8]. These risk factors are commonly found in elderly patients admitted to hospital and often several factors will be present in one patient.

The prevalence of hyponatraemia in our sample (6.9%) was lower than that found by Sunderam (11.3%) and diuretic-associated hyponatraemia (the presence of hyponatraemia in a patient prescribed diuretics, although not necessarily causally related) in our sample (3.4%) was also lower than the 7.2% found by Sunderam[6]. Borland and colleagues did not state the numbers of patients with hyponatraemia but the 95% confidence limits for mean serum concentrations of sodium and potassium in patients not on any diuretics (129-147 and 3.0-5.4 mmol/l) and on diuretics (127-147 and 2.8-5.7 mmol/l) were much wider than ours (suggesting a more heterogeneous group) although the means were similar to ours[10]. The relatively high prevalence in Sunderam's study may reflect differences in prescribing practice, in admission selection criteria (which are known to differ widely between Departments of Geriatric Medicine) or in blood test selection bias in his group. One problem in interpreting results in any cross-sectional study such as these, is the impossibility of corroborating the drug history and patient compliance. The drug history has been estimated as accurate in about one third of referrals to geriatricians in one study[11] with under-reporting of medication increasing with increasing numbers of co-prescribed drugs. We felt that a large study sample would show population trends even with occasional inaccurate drug histories.

We do not know how many patients aged over 65 in Wandsworth were admitted to hospitals other than the study hospital. It is conceivable that some more acutely ill patients were admitted by general physicians, thus affecting the case mix in our study group. However, this effect would occur in any district where a strict age-related policy was not in force; we feel that it is therefore reasonable to extrapolate our results to other departments with a similar admissions policy.

Our data are consistent with the hypothesis that patients admitted to hospital and who have been prescribed potassium-retaining diuretics with loop or thiazide diuretics are more likely to be hyponatraemic than patients not prescribed potassium-retaining diuretics. The small number of patients prescribed potassium-retaining diuretics alone (amiloride or spironolactone; $n=8$) makes it impossible to generalize about this group. It is of interest that although potassium-retaining diuretics are contraindicated in the presence of renal impairment and the potential danger of hyperkalaemia (probably greater than hypokalaemia) are well known[12], a significant number of patients in our study were receiving such drugs despite renal impairment. The serum urea (a reflection of renal function in the elderly) and the choice of potassium-retaining diuretics appeared to be the two major influences on serum potassium, and there was a small negative correlation with the serum sodium concentration; these effects were additive. There is an inverse relationship between sodium and potassium balance under the influence of aldosterone-sensitive sodium channels in the cortical collecting duct, and potassium-retaining diuretics all retain potassium at the expense of sodium probably by directly or indirectly acting upon this mechanism in the kidney[13]. Our findings are at least consistent with this basic physiology, although there are many more complexities of renal function and diuretic pharmacology which make precise predictions of drug effects in individuals impossible. In practice, severe hyponatraemia was a rare complication of diuretic therapy in our elderly patients. Interestingly there was not a significantly higher mortality in hyponatraemic patients (irrespective of cause) compared with those with normal serum sodium.

No cross-sectional study, however large, can prove a causal association especially when so many of the variables (diseases, treatments, age, renal function and so on) are inter-related. Relatively few prospective studies comparing the effects of different diuretics and different groups of elderly subjects have been published.

Any electrolyte disturbance will probably occur within the first three weeks of therapy with diuretics. It is not known precisely how diuretics induce hyponatraemia but at least three mechanisms are probably involved. First, diuretics directly inhibit urinary sodium chloride reabsorption in the loop of Henle and distal tubule. Second, volume depletion, caused by excessive natriuresis, will result in secondary non-osmolal anti-diuretic hormone (ADH) secretion. Third, potassium depletion may be produced by diuretic therapy and is associated with the compensatory movement of extracellular sodium ions into cells and possibly increased thirst. The first effect is less likely with loop diuretics than with thiazides because loop diuretics act in the loop of Henle, reducing sodium chloride reabsorption and thus diminishing the hypertonicity of the renal medullary interstitium. This results in decreased free water excretion for a given level of ADH activity in the collecting duct[14]. Scoble and colleagues have shown that amiloride exerts its potassium-sparing effect by blocking sodium reabsorption rather than by directly inhibiting potassium secretion[15]; excessive sodium loss from the distal convoluted tubule may contribute to hyponatraemia. In a prospective study, Friedman and colleagues showed that 11 elderly patients (eight female) who had recently been admitted to hospital with thiazide diuretic-associated hyponatraemia developed a significantly lower serum sodium concentration and osmolality than young or elderly

controls within 6 hours of a single oral dose of co-amilozide[16]. Friedman's study showed that the cause of the acutely-induced experimental hyponatraemia in this highly selected group was probably free water retention rather than sodium depletion. In one patient, fluid restriction during re-challenge with co-amilozide initially prevented hyponatraemia, but the serum sodium fell after free fluid intake was allowed. The normal maximum capacity of the kidney to excrete free water is approximately 10-20 litres per day, so significant net water retention (and hence hyponatraemia) cannot occur without concomitant ADH activity. The effect of age on this mechanism is not known. It is also not known whether thiazide diuretics or amiloride (or the two combined) is the important factor in the genesis of net water retention and/or sodium loss in some old people, nor why a few individuals seem to be particularly susceptible. Both salt depletion and water overload can be present[17].

The information obtained about prescriptions in the community is difficult to interpret. It is notoriously hard to obtain accurate information about prescribing habits in the local community although national figures may be representative of prescribing practice[11,18]. The data we obtained were for patients of all ages, and thus not directly comparable with the inpatient group of elderly patients. It is likely that there is disparity in the type of diuretics prescribed for younger patients. The use of thiazides for hypertension is likely to be more common in the young; the increased prevalence of heart failure and renal impairment with age could make the use of loop diuretics more frequent in the elderly.

The difference in relative prescribing rates of various diuretics between patients admitted to hospital and those in the community are likely to be due to a number of factors. These factors would include a difference in case-mix and differences in the demographic variables in the two populations. In both populations the level of compliance is unknown. Uncertainty about compliance is possibly the major flaw of any study examining the effects of diuretics without using any objective method of assessing compliance. The large numbers of patients which we examined might have diluted this effect; the fact that the results are plausible and broadly agree with Borland's results supports but does not prove this. It remains important that the prevalence of co-amilozide prescription in the community was greater than any other combination diuretic, and relatively greater than in the inpatient group. This fact alone would render untenable any inference concerning co-amilozide's specific causal relationship with the genesis of hyponatraemia from our data. Without a prospective study using a control group, the causality of any association is purely speculative.

We conclude that during diuretic therapy the use of potassium-sparing diuretic combinations may be associated with higher serum potassium concentrations than if potassium supplements or no potassium sparing therapy is used. However, the price paid for this possible benefit is that potassium-retaining diuretics may be associated with an increased risk of hyponatraemia. These disturbances tend to be modest and only rarely (and currently, unpredictably) serious, although renal impairment increases the risk. There is insufficient evidence from our study to criticise any one fixed combination preparation, in particular co-amilozide, which was the most commonly prescribed thiazide/potassium-retaining diuretic combination in the community from which our patients came. Further prospective studies need to be undertaken in this patient group to ascertain the relative attributable risk of metabolic disturbance by diuretics, both alone and in combination. We also need to establish how to identify those individuals who are at risk of developing severe hyponatraemia with diuretics. Although electrolyte disturbances are usually modest, biochemical monitoring remains necessary for elderly inpatients who have had diuretics prescribed to identify those patients at risk of more serious complications.

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